Hypertension Research (2018) 41, 1–5

www.nature.com/hr

REVIEW SERIES

The impact of salt intake during and after pregnancy

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Although high blood pressure before pregnancy is associated with a risk of gestational hypertension and preeclampsia, no convincing evidence has been produced to show that dietary salt reduction helps in the prevention and treatment of hypertension during pregnancy. Thus the current guidelines do not recommend a sodium restriction during pregnancy to prevent gestational hypertension and the development of preeclampsia. However, the long-term impact of hypertensive disorders of pregnancy for life-threatening diseases later in life is a critical issue. Gestational hypertension could contribute to the risk of developing hypertension later in life, and recent studies have suggested that gestational hypertension and preeclampsia are linked to cardiovascular complications. In this article, we provide an overview of the current perspectives on the salt intake of pregnant women and consider both the short-term influence and the impact beyond the perinatal period.
Hypertension Research (2018) **41,** 1–5; doi:10.1038/hr.2017.90; published online 19 October 2017

Keywords: chronic hypertension; dietary salt; gestational hypertension; hypertensive disorders of pregnancy; preeclampsia

INTRODUCTION

High blood pressure before pregnancy is associated with a risk of gestational hypertension and preeclampsia,[1,2] and fertile women with chronic hypertension are encouraged to keep their dietary sodium intake low to prevent their blood pressure from increasing.[3] However, the current guidelines[3–6] do not recommend a sodium restriction during pregnancy to prevent gestational hypertension and the development of preeclampsia. The World Health Organization Guideline Development Group dared to state that the group considered the avoidance of an 'excessive' dietary salt intake as a healthy dietary practice, whereas sodium restriction during pregnancy was not recommended for the purpose of preventing the development of preeclampsia and its complications.[4]

Clinicians have long recommended the restriction of the dietary salt intake to prevent sodium and water retention, which can lead to the development of preeclampsia.[7] Later (but still decades ago), sodium restriction was considered a trigger of overt eclampsia among women with preeclampsia,[8] and extra salt was considered essential for the health of pregnant women.[9,10] More recent studies have established long-term cardiovascular risk in women with a history of preeclampsia[11,12] and those with gestational hypertension.[13] In the present article, we provide an overview of the current issues on the salt intake of pregnant women and consider both the short-term influences and the impact beyond the perinatal period.

HISTORICAL ASPECTS OF THE ISSUE OF SALT INTAKE DURING PREGNANCY

Sodium retention with an increase in the circulating plasma volume is observed during normal pregnancy,[14,15] whereas intravascular volume depletion may be associated with a relative sodium deficiency among women with preeclampsia.[9] Salt has been shown to cure eclampsia in a large percentage of cases, and it has been shown that the administration of salt to cure convulsions has little risk of causing toxemia during pregnancy.[10] In a study that included 2019 pregnant women, Robinson[10] found that the prevalence of preeclampsia was approximately 2.6 times higher in women who were advised to reduce their salt intake in comparison to those who were told to increase their salt intake (for example, by adding extra salt to their food at the table or eating salty bacon or fish). The investigator further reported that all of the 20 women with preeclampsia who were treated with extra salt (16 of the patients took an extra 200–300 g sodium chloride daily) improved in a dose-dependent manner (a larger dose was associated with a quicker and more complete recovery).[10] The infusion of a stable plasma protein substitute produced a transient 17/15 mm Hg reduction in the systolic/diastolic blood pressure of 9 pregnant women with hypertension.[16] In 1970, Palomaki and Lindheimer[8] reported that the restriction of dietary sodium intake to 17 mEq (1 g) per day was associated with a worsening of the renal function in a preeclampsia patient, which was recovered with a sodium intake of 206 mEq (12 g) per day. They stated that classic observations concerning the consistent benefits of avoiding salt during pregnancy may be misleading.[8] On the contrary, a sodium overload of 3–6 g per day resulted in lower blood pressure in a pregnant woman with chronic hypertension.[9] In contrast to the non-pregnant state, increasing salt intake was shown to reduce blood pressure in pregnant women.[17] Although the aldosterone level in normotensive pregnant women was spontaneously high, irrespective of the salt intake, the 24-h ambulatory blood pressure remained low despite high aldosterone availability and a high-salt intake.[17]

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Received 8 June 2017; revised 27 June 2017; accepted 28 June 2017; published online 19 October 2017

The previous systematic review did not demonstrate any evidence of the benefits of a low-salt intake during pregnancy,[18] and no significant difference was observed in the development of preeclampsia between women with a low-salt intake and those with a normal salt intake during pregnancy (2 trials; relative risk, 1.11; 95% confidence intervals, 0.46–2.66). Furthermore, the risk of the development of gestational hypertension did not differ to a statistically significant extent (1 trial; relative risk, 0.98; 95% confidence intervals, 0.49–1.94).[18] Until recently, no convincing evidence has been produced to suggest that dietary salt reduction helps in the prevention or treatment of hypertension during pregnancy.[19,20] Dietary salt restriction during pregnancy is therefore not recommended by clinical guidelines in a number of countries.[3–6] Nevertheless, the National Institute for Health and Clinical Excellence (NICE) Guideline Development Group stated that 'this does not diminish the importance of an awareness of salt intake in a healthy lifestyle or of advising dietary salt reduction in chronic hypertension'.[3]

THE YANOMAMI, AN ABORIGINAL TRIBE OF THE AMAZON

The Yanomami (Yanomama or Yanomamo), which denotes a human being in their language, is considered to be a representative unacculturated population. Their sodium intake is extraordinarily low—in the order of 1 mEq per day.[21,22] This population has been frequently referred to as having a low prevalence of hypertension or to be free from hypertension. The blood pressure values of the Yanomami people increase from the first to second decade but do not systematically increase during the subsequent years of life.[21] To compensate for low sodium intake, their plasma renin activities and aldosterone excretions are extremely elevated; the aldosterone excretion of 11 Yanomami participants was reported to be 27.3–164.9 μg per day, which is markedly higher than the upper limit of Caucasians (17.3 μg per day).[21] Although the long-term effects of a low sodium intake on their health have not been evaluated, as the mean life expectancy of Yanomami Indians is approximately 40 years,[21,23] investigators have inferred that maintaining a low blood pressure via a low sodium intake would prevent cardiovascular complications.

Similar to adults, the renin–angiotensin–aldosterone system (RAAS) of pregnant Yanomami women was shown to be markedly enhanced, which would contribute to maintaining their body's sodium balance.[22] Mothers and infants in this culture appear healthy, with no evident disadvantage from their dietary pattern.[22] However, we would like to mention an unusual custom of Yanomami women: after giving birth, Yanomami women (at an average of 14 years of age) decide whether or not their child should live. If they decide that the child should not live, then the child's life is ended by the mothers themselves. Although this practice of infanticide by the Yanomami is of philosophical interest to us, we should be cautious in applying perspectives obtained from the Yanomami to other acculturated populations.

THE PHYSIOLOGICAL MECHANISMS IN RELATION TO SODIUM IN PREGNANCY

Preeclampsia develops with increasing frequency as a pregnancy approaches term.[20] Unfortunately, preeclampsia is not observed in mammalians other than humans and some primates because of substantive differences in physiology; in particular, trophoblast invasion is very limited in mice, and the transformation of the uterine arteries depends on maternal factors.[24] Attempts to develop a useful animal model of preeclampsia[25] will help to more fully elucidate the mechanism, prevention and treatment of preeclampsia in the future. Hitherto, the physiological mechanism in normal and abnormal pregnancies has been investigated and is introduced in this review series.[26,27] We briefly overview the physiological aspects in relation to sodium during pregnancy.

A high-salt intake was shown to impair brachial artery flow-mediated dilatation, which was observed in the postprandial stage[28] and after 1 week of salt loading.[29] Low flow-mediated dilatation was observed among women with preeclampsia and remained for 3 years postpartum,[30] which suggested that the endothelial dysfunction precedes the onset of preeclampsia and remains even after delivery.[26,30] Five days of salt loading in healthy adults reduced the plasma levels of nitrate and nitrite independent of the blood pressure response.[31] The development of early preeclampsia is associated with an altered nitric oxide metabolism and/or altered nitric oxide synthesis.[32]

Oxidative stress has a key role in the development of endothelial dysfunction.[33] Savvidou *et al.*[34] demonstrated that the endothelial function of pregnant women who developed preeclampsia was impaired before the development of the clinical syndrome, and women with impaired placental perfusion (identified by a Doppler waveform) had significantly high plasma concentrations of asymmetric dimethylarginine, which was partly associated with endothelial dysfunction.[34] The mechanisms of endothelial dysfunction involve the release of soluble fms-like tyrosine kinase (sFlt-1), which is also known as soluble vascular endothelial growth factor (VEGF) receptor-1 (sVEGFR-1).[33] sFlt-1 is a circulating antiangiogenic protein and an endogenous inhibitor of VEGF and enhances the endothelial dysfunction already established by oxidative stress, reactive oxygen species and damage.[33] The levels of sFlt-1 increase in women with preeclampsia and disrupt VEGF, which is established before the manifestation of the disorder.[33] As Redman *et al.*[35] discussed, angiogenic and antiangiogenic factors of placental origin may contribute to preeclampsia. Furthermore, placental ischemia and reperfusion further contributes to oxidative damage, mainly through the conversion of xanthine dehydrogenase to xanthine oxidase,[33] and subsequent inflammation due to placental oxidation stress can lead to endothelial dysfunction. Sodium overload is reported to increase oxidative stress in various organs,[36,37] and it would also affect oxidative stress in the placenta. It is noteworthy that low-dose aspirin is effective for preventing preeclampsia,[38,39] which may be because aspirin inhibits the production of superoxide by neutrophils.[40]

Excess sodium chloride may affect the adaptive immune system via serum/glucocorticoid regulated kinase 1 signaling.[41] Modest increases in the concentration of sodium chloride markedly enhanced type 17 helper T (Th17) responses *in vitro*, as did a high-salt diet *in vivo*.[42,43] These high-salt conditions in the lymphoid tissues may be essential for an optimal adaptive immune response during infection because the sodium concentrations in the interstitium and lymphoid tissues are 160–250 mmol l^{-1} when plasma sodium concentration is approximately 140 mmol l^{-1}.[44] In contrast, and probably to compensate for the activation of immune regulation,[42–44] a high-salt diet would be linked to autoimmune diseases caused by a disturbance in immune homeostasis (for example, rheumatoid arthritis and multiple sclerosis[45]) through the induction of Th17 cells.[42] Interestingly, and different from the pro-inflammatory Th17 cells, Binger *et al.*[46] reported that a high-salt intake reduces non-inflammatory innate immune cell activation, including alternative activated M2 macrophages, which are induced by interleukin-4 and interleukin-13. Based on these differential effects on immune cell activity, investigators hypothesize that sodium chloride may shift the overall balance of the immune system.[45,46] This salt-regulatory concept can also be applied in normal pregnancy and to the changes observed in preeclampsia.[47]

A paradoxical hyperactivation of RAAS with an increase in the circulating plasma volume is observed among normal pregnant women,[48,49] and a blunt response of the blood vessels to angiotensin II would support placentation. However, RAAS is suppressed with the reduction of the circulating plasma volume in women with preeclampsia.[50] Therefore, enhanced vascular reactivity to angiotensin II is observed. A reduction in the secretion and utilization of aldosterone leads to insufficient placental development. Furthermore, in women with hypertensive disorders of pregnancy, increased sodium reabsorption at the ascending loop of Henle and the distal collecting duct in the kidney and the production of agonistic autoantibodies against angiotensin II type 1 receptor may result in the suppression of renin. A higher urinary excretion of immunoreactive plasmin(ogen) and the plasmin-dependent activation of ENaC in urine were also reported among women with preeclampsia.[51] Mishra *et al.*[40] reported that the vascular reactivity to angiotensin II was enhanced in the omental arteries of women with preeclampsia in comparison to normal pregnant women; it was assumed that this could be attributed to the activation of reactive oxygen species. Sodium can mediate these pathways, and these mechanisms would be linked to salt-sensitive hypertension, which is more frequently observed among women with metabolic disorders or obesity.[52,53] In addition, increased circulating soluble adhesion molecule E-selection, von Willebrand factor, endothelin-1 and 24-h urinary albumin excretion levels were observed in individuals with salt-sensitive hypertension.[54]

BLOOD PRESSURE BEFORE AND DURING PREGNANCY

High blood pressure and other cardiovascular risk factors before pregnancy are associated with a risk of gestational hypertension and preeclampsia.[1,2] Women with chronic hypertension are also at risk of short-term postpartum complications, such as pulmonary edema and renal failure.[55] Thus blood pressure in fertile women should be evaluated before conception, and if not, it should be evaluated at the time of the first prenatal visit. Reducing or substituting the dietary sodium intake can reduce blood pressure, at least in the short term.[23]

The blood pressure of pregnant women is typically decreased during mid-pregnancy and steadily increases during the third trimester.[56] This transient decrease in blood pressure can be explained by the primary peripheral arterial vasodilation with relatively less arterial circulation, which occurs in the early stage of pregnancy[57] and also leads to the enhancement of cardiac output and secondary to afterload reduction, the stimulation of RAAS and vasopressin release and renal sodium and water retention with the expansion of the extracellular fluid and plasma volume compartments.[57] We clearly demonstrated such blood pressure trends among normal pregnant women based on self-measured home monitoring in the Babies and their Parents' Longitudinal Observation in Suzuki Memorial Hospital in Intrauterine Period study.[58] However, the Avon Longitudinal Study of Parents and Children study investigators reported that women who developed gestational hypertension or preeclampsia had higher blood pressure from very early in pregnancy and that a reduction of the initial decline in systolic blood pressure occurred during the second trimester.[1] We can safely state that the reduction of mid-pregnancy blood pressure decline is associated with high-salt sensitivity because such pregnant women have been reported to have a family history of hypertension,[56] obesity in early pregnancy[56] and gestational weight gain.[56] Such disorders can be an early marker of hypertensive disorders,[59] placenta-mediated diseases (including preeclampsia and fetal growth restriction)[1,60,61] and preterm birth.[61] Premenopausal women with a history of severe preeclampsia are comparably salt sensitive,[11] and salt sensitivity may be more likely among pregnant women without a typical mid-pregnancy alteration. Meanwhile, Veerbeek *et al.*[62] inferred that the number and levels of postpartum-modifiable cardiovascular risk factors differed between patients with early- and late-onset preeclampsia, and patients with other hypertensive disorders of pregnancy, women with early-onset preeclampsia, showed an overall less favorable risk profile in comparison to those with late-onset preeclampsia. This was particularly reflected in their glucose and lipid levels.[62]

THE EFFECTS OF HYPERTENSION AND SODIUM ON COMPLICATIONS AFTER PREGNANCY

Currently, chronic (preexisting) hypertension is defined as hypertension that presents either prepregnancy or that develops at <20 weeks gestation.[5,6] Gestational hypertension is defined as hypertension that is first identified at $\geqslant 20$ weeks of pregnancy, and the presence of gestational hypertension with newly raised proteinuria or one or more adverse conditions is defined as preeclampsia. As stated in this review series by Ohkuchi *et al.*,[27] the term 'pregnancy-induced hypertension' is no longer used because of its unclear meaning in clinical practice.[6] Instead, 'hypertensive disorders of pregnancy' is used to describe chronic hypertension, gestational hypertension, preeclampsia or other hypertensive effects based on different diagnostic and therapeutic considerations; this definition naturally includes women with superimposed preeclampsia (that is, chronic hypertension in association with preeclampsia).[5,6,27]

An advantage of the self-measurement home blood pressure is that it would contribute to improving outcomes of pregnant women[63,64] and their offspring.[65–67] The American College of Obstetricians and Gynecologists[5] suggests the additional weekly measurement of home blood pressure for pregnant women with gestational hypertension. Although maternal gestational hypertension does not affect the home blood pressure in the offspring, it has been shown to strongly affect the maternal home blood pressure and even 7 years after giving birth.[65] Inoue *et al.*[68] recently investigated urinary salt excretion and the perinatal outcomes in relation to home blood pressure. Their study population included 184 pregnant women, including 14 who developed hypertensive disorders. The average urinary salt excretion was not significantly associated with the development of hypertensive disorders of pregnancy ($P=0.90$) or with the likelihood of the birth of light-for-date infants (exact data unavailable). However, higher systolic and diastolic home blood pressures were found to be significant predictors for hypertensive disorders of pregnancy based on a multivariable-adjusted logistic model (the units for the odds ratios were unclear; $P<0.0001$). The urinary salt excretion observed in their study (5–13 g per day)[68] was unlikely to be related to deleterious outcomes for either the mothers or their infants. The accurate classification of blood pressure level based on home monitoring may help to identify novel prognostic factors and appropriate treatment.[64] Further research should assess the impact of salt intake on the home blood pressure of pregnant women.

In addition to pregnant women, there is still a debate as to whether the strict restriction of sodium intake is beneficial[69] or harmful[70,71] among various populations. Our meta-analysis demonstrated that there is no robust evidence suggesting that the long-term reduction of the salt intake would prevent chronic kidney disease or delay its progression.[72] A recent technical report raised a fundamental issue with regard to the feasibility of achieving a sustained low sodium intake in free living individuals.[23] The report supports interventions to reduce the sodium intake in populations in which >5 g of sodium (>12.5 g of salt) is consumed per day but are not supportive for reducing sodium intake in populations in which <3 g of sodium

(<7.5 g of salt) is consumed per day, which is mainly because of the lack of large randomized controlled trials.[23] The age-standardized estimated sodium intake in Japan was 4.71 g (11.8 g of salt) in 1990 and 4.89 g (12.2 g of salt) in 2010.[73] These average values of the population are at the upper limit of the range recommended by the technical report,[23] and many Japanese consume more salt. Although the life expectancy in Japan is one of the longest in the world, dietary salt restriction would be an effective low-cost strategy for the Japanese population, and this strategy may also be applicable for fertile women. Meanwhile, the average level for adjusted 24-h urinary sodium excretion among pregnant Japanese women at approximately 20 weeks of gestation was 3.1 g (7.7 g of salt) in our cohort[74] and 3.4 g (8.6 g of salt) in another population[68]; this would be due to dietary restriction.[74] How this comparably low level of average salt intake affects the cardiovascular prognosis of pregnant women should be investigated in future studies.

The impact of hypertensive disorders of pregnancy on short-term complications in mothers and offspring is a major issue, and its long-term impact on life-threatening diseases is another concern. Gestational hypertension would contribute to the risk of developing hypertension later in life,[5] and recent studies have delineated a link between preeclampsia and cardiovascular complications.[11,75] Martillotti *et al.*[11] reported that 2 of the 21 women with a history of preeclampsia and no other identifiable risk factors experienced myocardial infarction before menopause. Although the guidelines[3–6] do not recommend interventions regarding dietary salt for the prevention or management of preeclampsia, the management of dietary salt can be an influential strategy with regard to the long-term risk of cardiovascular disease (even in pregnant women). Subsequent lifestyle education and management, and in some cases intervention for women and their offspring, is much more essential.

In conclusion, women with chronic hypertension are encouraged to keep their dietary sodium intake low, either by the reduction or substitution of dietary sodium, to reduce their blood pressure.[3] In addition to women with high blood pressure, dietary sodium restriction may be beneficial for normotensive women hoping to give birth, especially those who display salt sensitivity (that is, women with metabolic disorders or obesity, which is linked to multiple risk factors).[52,53] Although the reported paradoxical impact of a higher sodium intake for lowering blood pressure in patients with pre-eclampsia and eclampsia[9,17] should be noted, physicians and health-care providers should consider the natural history of individuals with hypertension, irrespective of whether they are pregnant or have given birth, and consider their long-term future.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

YI received research support from Omron Healthcare

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